

REMARKS

A Petition for Extension of Time is being concurrently filed with this Amendment. Thus, this Amendment is being timely filed.

Applicant respectfully requests the Examiner to reconsider the present application in view of the foregoing amendments to the specification and claims and the following remarks.

Status of Claims

In the present Amendment, claims 1 and 3 have been amended, and claim 4 has been added. Also, claim 2 has been canceled herein without prejudice or disclaimer of the subject matter contained therein. Thus, claims 1, 3 and 4 are pending.

Support for the amendment to claim 1 can be found in the last line of paragraph [0006] of the publication of the present application (U.S. Application Publication No. 2006/0251719) (see also page 3, lines 1-3 of the non-published specification). Support for the amendment to claim 3 can be found in Examples 3 and 4 of the present application (see also page 3, lines 3-7 of the non-published specification). No new matter has been added with these amendments.

Claim 4 has support at page 13, second full paragraph. No new matter has been added.

Based upon the above considerations, entry of the present amendment is respectfully requested.

In view of the following remarks, Applicant respectfully requests that the Examiner withdraw all rejections and allow the currently pending claims.

Objection to Specification

At page 2, paragraph 4 of the Office Action, the Examiner objects to the present specification at page 25 which refers to Figure 6. Applicant notes that the specification has been appropriately amended to correct the typographical error (wherein the open circle represents the untreated group). Further, support for the amendment is supported by the original PCT application and thus no new matter has been added.

Issues Under 35 U.S.C. § 112, Second Paragraph

Claim 3 is rejected under 35 U.S.C. § 112, second paragraph, as being incomplete for omitting an essential step (see paragraphs 5-6 of the Office Action). Applicant respectfully traverses.

Claim 3 is amended herein to incorporate the step for administering the sustained-release preparation containing the hydrogel. Thus, Applicant respectfully submits that this rejection has been overcome. Reconsideration and withdrawal of this rejection are respectfully requested.

Issues Under 35 U.S.C. § 102

Claims 1-2 stand rejected under 35 U.S.C. § 102(b) as being anticipated by **Ikada et al.** (JP 08-325160 (see paragraphs 7-8 of the Office Action)).

Also, claim 3 stands rejected under 35 U.S.C. § 102(b) as being anticipated by **Chvapil '088** (U.S. 4,485,088) (see paragraph 9 of the Office Action).

Applicant respectfully traverses, and reconsideration and withdrawal of these rejections are respectfully requested.

The Present Invention and Its Advantages

The present invention is directed to a sustained-release preparation which comprises a drug and a gelatin hydrogel, wherein a concentration gradient of the drug is formed within the hydrogel (see pending claim 1 herein). The present invention is also directed to a method of using the sustained-release preparation (see pending claim 3).

As described in the specification at page 3, lines 9-19, in the present invention, the drug interacts with the gelatin hydrogel and therefore the drug cannot freely disperse in the hydrogel. This means that the drug is not released until the hydrogel itself is degraded and the polymer becomes water-soluble. Also, the concentration gradient of the drug is formed within the hydrogel, which enables a larger amount of the drug to be released from the drug-rich side of the hydrogel (versus the drug-lean side). Thus, the present invention has the advantage of a sustained release of the drug with control of direction of the drug release.

Claims 1 and 2

In paragraph 8 of the outstanding Office Action, the Examiner states: "Since the gelatin gel will swell and degrade in the presence of water (or body fluid), the concentration of the drug in the gel will change and consequently a concentration gradient of the drug in the gelatin gel will be formed." Further, the Examiner refers Applicant to the Abstract, paragraph [0005] and claim 11 of Ikada *et al.* as disclosing the features of instantly pending claims 1-2.

However, Applicant respectfully submits that the present invention has been misunderstood. The cited Ikada *et al.* reference does not (inherently or intrinsically) disclose all

instantly claimed features. It appears that the Examiner likely envisages that the release of drugs occurs via a conventional *diffusion* mechanism(s).

In the case of a conventional diffusion mechanism, when the drug is released from a surface of a substrate, the drug present in the inner portion of the gel moves toward the drug-lean portion via diffusion. A concentration gradient may be transiently created but will soon disappear as the drug moves within the gel. Even if a concentration gradient is present for a short period of time, the gradient is such that the surface portion is drug-lean (or poor) and the inner portion is drug-rich. With this type of concentration gradient, the direction of the drug release cannot be controlled.

In contrast, the characteristic feature of the gelatin hydrogel of the present invention is that the drug is entrapped (sustained) within the hydrogel via a physical interaction, for example an electrostatic interaction. The drug will be released only from the portion where the gelatin hydrogel is degraded, while the drug entrapped in the gel will not move within the gel itself. Again, the present invention has the advantage of a sustained release of the drug with control of direction of the drug release wherein Ikada et al. does not disclose such a feature.

Such a nature of the gelatin hydrogel is well described in the specification. For example, page 1, paragraph [0015] of the published '719 application describes how the hydrogel of the present invention forms a complex through physicochemical interaction and will decompose by hydrolysis or enzymatic degradation:

As used herein, the bioabsorbable polymer used for producing a bioabsorbable polymer hydrogel is a polymer which can form a complex through physicochemical interaction with the drug to effect sustained release, and which will be decomposed by hydrolysis and oxygen decomposition in vivo, or will be

hydrolyzed by an action of a biologically active substance such as an enzyme present in the living body.

In addition, the present invention is characterized in that the release of the drug can be controlled according to the decomposition properties of the hydrogel. For example, as described at page 2, paragraph [0017] of the '719 specification:

In order to achieve a more excellent effect to control sustained-release of a drug according to the invention, it is preferable that the bioabsorbable polymer hydrogel is made to be insoluble in water, whereby the release of the drug may be controlled according to the decomposition properties of the bioabsorbable polymer hydrogel *in vivo*. More specifically, the sustained release rate of a drug may be controlled by decomposition of the bioabsorbable polymer hydrogel *in vivo*.

Also, the '719 specification at page 1, a part of paragraph [0015] refers to the drug-gel complex:

...A derivative as used herein refers to a substance modified to be suitable to form a complex of the drug and the bioabsorbable polymer hydrogel. Specific examples include derivatives having a guanidyl group, a thiol group, an amino group, a carboxyl group, a sulfuric acid group, a phosphoric acid group, or a hydrophobic residue such as an alkyl group, an acyl group or a benzyl group, and a low molecular hydrophobic substance or the like introduced therein.

As shown in the above descriptions, the drug entrapped within the gelatin hydrogel does not move within the gel via diffusion. In contrast, a gradient of drug concentration will not be made within the gel of Ikada *et al.* Further, Ikada *et al.* does not inherently disclose the present invention. In this regard, anticipation requires that "each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949 (Fed. Cir. 1990) (citing *Verdegaal Bros., Inc. v. Union Oil Co.*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987)). Here, the cited Ikada *et al.* reference fails to disclose all instantly claimed features. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

Claim 3

The cited Chvapil '088 reference is related to a treatment of fibrosis during wound healing using hydrophilic hydrogel which allows the drug to be penetrated across the skin barrier. It only shows that when a hydrogel containing a drug is applied on a skin, the drug is detected in the urine of the subject. Chvapil '088 draws a conclusion that the drug is constantly released. In this experiment, however, the drug appears into be simply impregnated into the hydrogel, and the drug is released via diffusion.

In such a system, as the drug is released from the surface of the gel, the drug present in the inner portion of the gel will move toward the surface of the gel. Thus, no gradient of the drug concentration will be made or maintained within the Chvapil '088 gel. At the same time, Chvapil '088 has the disadvantage of the release speed at the application site decreasing.

In contrast to Chvapil '088, in the sustained-release preparation of the present invention, the drug entrapped in the hydrogel will be released only from the decomposed portion of the gel, and the concentration of the drug in each portion of the hydrogel remains the same from the initial concentration. In addition, the hydrogel of the invention does not release the drug at a constant rate. In other words, Chvapil '088 does not disclose all features of instantly pending claim 3 of the present application.

Another important feature of the present invention, as mentioned above, is that the concentration gradient of the drug is formed in the gel so that the direction of the drug release can be controlled. A higher concentration of the drug is released from the drug-rich side and a lower concentration is released from the drug-lean side of the gel. This is well supported by the

description of the present specification as mentioned above (see in particular Example 3). Such a feature and advantage is not disclosed in Chvapil '088.

Thus, under *Robertson* and *Verdegaal Bros.*, this rejection has been overcome. Chvapil '088 does not disclose or suggest a sustained-release preparation of the present invention in which a concentration gradient of the drug is formed within the hydrogel. Reconsideration and withdrawal of this rejection are respectfully requested.

Issues of Obviousness-Type Double Patenting

Claims 1-2 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of copending Application No. 10/484,023 (referred to as the '023 application hereinafter) (see paragraphs 10-11 of the Office Action).

Also, claims 1-2 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of copending Application No. 10/528,998 (the '998 application) (see paragraph 12 of the Office Action).

Further, claims 1-2 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of copending Application No. 10/551,497 (the '497 application) (see paragraph 13 of the Office Action).

Applicant respectfully traverses, and reconsideration and withdrawal of these rejections are respectfully requested.

As mentioned, the present invention is directed to a sustained-release preparation which comprises a drug and a gelatin hydrogel. The present invention is characterized in that a concentration gradient of the drug is formed within the hydrogel, which enables a larger amount

of drug to be released from the drug-rich side of the hydrogel versus the drug-lean side of the gel, whereby the direction of drug release can be controlled.

Claim 1 of each of the cited '023, '998 and '497 applications does not render claim 1 of the present application as obvious. This is because the cited claims of the '023, '998 and '497 applications do not have a drug concentration gradient as achieved by the present invention. The drug entrapped within the '023 / '998/ '497 gelatin moves via diffusion (similar to the cited Ikada *et al.* reference mentioned above). However, in the present invention, the direction of drug release is controlled and the drug is entrapped in the gel such that it will not move within the gel (i.e., no diffusion).

Thus, these provisional rejections have been overcome. Reconsideration and withdrawal of these rejections are respectfully requested.

In the alternative, Applicant requests the Examiner to hold these rejections in abeyance (as they are provisional) until this application or the cited application(s) issues as a patent.

Conclusion

A full and complete response has been made to all issues as cited in the Office Action. Applicant has taken substantial steps in efforts to advance prosecution of the present application. Thus, Applicant respectfully requests that a timely Notice of Allowance issue for the present case.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Eugene T. Perez (Reg. No. 48,501)

at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.147; particularly, extension of time fees.

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Respectfully submitted,

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